Radiological Diagnosis of Hepatocellular Carcinoma

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In 2011, it is estimated that 20,000 deaths occurred because of cancer of the liver or intrahepatic bile ducts; thus, this is the fifth most common cause of cancer deaths in men and the ninth most common in women.[1] Over the next decade, the number of patients with hepatocellular carcinoma (HCC) is anticipated to increase as the population of baby boomers with hepatitis C ages and as the prevalence of cirrhosis from nonalcoholic fatty liver disease rises with the well-recognized obesity epidemic in the United States.[2] Establishing the diagnosis of HCC is unique in comparison with many other malignancies because biopsy may not be necessary to make the diagnosis. In comparison with other cancers for which "tissue is the issue," in many circumstances, the specificity of imaging characteristics may be sufficient to establish the diagnosis of HCC.

In the United States, HCC usually occurs in the setting of cirrhosis, although this is not always the case, with the classic example being HCC associated with hepatitis B in the noncirrhotic liver. Because HCC typically occurs in cirrhotic livers, accurate diagnostic imaging criteria are needed to differentiate HCCs from other nodules or lesions that may develop in patients with cirrhosis (Table 1). Ultrasound is used to screen patients with cirrhosis for HCC, and if a nodule $\geq$ 1 cm is seen on ultrasound, American Association for the Study of Liver Diseases guidelines recommend contrast-enhanced cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the nodule.[3] Although contrast-enhanced ultrasound is not approved in the United States, it is used in many parts of the world as a diagnostic imaging tool. However, the limitations of contrast-enhanced ultrasound are well recognized and include its limitations in anatomic coverage, its dependence on the operator, and its limitations in distinguishing HCC from peripheral cholangiocarcinoma.[4]

When Is Imaging Alone Adequate for Diagnosing HCC, and When Is Biopsy Needed?

Two organizations have developed diagnostic imaging and classification criteria for HCC: the Organ Procurement and Transplantation Network (OPTN), which is administered through the United Network for Organ Sharing (UNOS), and the American College of Radiology with its liver imaging reporting and data system (LI-RADS).[5,6] In 2008, UNOS, the organization that manages organ transplants in the United States, organized a consensus meeting on HCC.[5] A goal of the meeting was to develop and recommend better diagnostic imaging criteria to increase the specificity of an HCC diagnosis and to determine in which cases imaging alone would suffice for the diagnosis without the need for liver biopsy. The imaging criteria still in effect at the time were vague and required a lesion "corresponding to a vascular blush" seen on CT or MRI. Developing better imaging criteria is critically important because approximately 20% of liver transplants performed in the United States are for unresectable HCC.[7] Furthermore, a study of the UNOS database demonstrated that 21% of patients who underwent transplantation in the United States with Model for End-Stage Liver Disease (MELD) exception points for HCC (untreated) did not have HCC on explant.[8] These patients who underwent transplantation with HCC MELD exception points and did not have HCC on explant had either no lesions or benign lesions (Table 1). Also, the increasing incidence of peripheral cholangiocarcinoma in this patient population, which may retain contrast during the portal venous phase

Abbreviations: ACRIN, American College of Radiology Imaging Network; CT, computed tomography; HCC, hepatocellular carcinoma; LI-RADS, liver imaging reporting and data system; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.

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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.114

(versus the washout of contrast seen during this phase with HCC), is a particular concern.[4]

The UNOS imaging group proposed imaging characteristics for diagnosing HCC without the need for liver biopsy based on single-center studies demonstrating specific imaging characteristics with high specificity (>90%-95%) for diagnosing HCC with histology as the gold standard[3,9] (Table 2). LI-RADS has also established CT and MRI criteria for diagnosing HCC without the need for biopsy. Although there are differences between the OPTN and LI-RADS criteria, they share the common features of arterial enhancement with portal venous washout, and each has growth rate criteria for HCC (Figure 1, Table 2). Notably, nodules less than 1 cm cannot be classified as HCC by imaging alone, and alpha-fetoprotein is not part of the diagnostic criteria. When radiologists are interpreting images from liver transplant candidates, they are required to use the OPTN criteria and should state the number of HCCs, measure the largest diameter of each tumor, state the segment in which the lesion or lesions are located, and stress whether the patient is within the Milan criteria. In addition to the proposed imaging characteristics, UNOS also requires minimal technical specifications for CT and MRI.[10,11] Implementation of the imaging criteria and technical specification requirements is pending the finalization of the Web-based entry system. Transplant centers have a short remaining time window for incorporating the new policy into their clinical routine to ensure compliance by the time the new policy is implemented.

Biopsy of liver nodules may be indicated when a nodule does not meet imaging characteristics for HCC. It is important to keep in mind that 5% to 10% of HCCs, such as iso/hypovascular HCCs, may not meet the imaging criteria for HCC. For liver transplant candidates who have a liver nodule that does not meet OPTN class 5 imaging criteria, a biopsy-proven diagnosis is needed to receive HCC MELD priority for liver transplantation. Keep in mind that not all OPTN class 5 lesions will qualify for automatic HCC MELD exception points, and the majority of patients with HCC are not liver transplant candidates (centers in certain regions of the country may perform transplantation for patients with HCC initially beyond the Milan criteria and have down-staging protocols). If a patient is not a liver transplant candidate and does not meet the OPTN imaging criteria for HCC, then the role of biopsy is not driven by MELD priority for HCC. Thus, although it may be prudent to proceed with the biopsying of a nodule that

TABLE 1: Examples of Nodules and Lesions That Occur in Cirrhotic Livers and Need to Be Distinguished From HCC

Regenerative nodules
Confluent fibrosis
Arteriovenous shunting
Dysplastic nodules
Peripheral cholangiocarcinomas
Atypical hemangiomas

TABLE 2: Diagnostic Imaging Criteria for HCC

OPTN	LI-RADS
Six categories range from a nondiagnostic study (OPTN class 0) to meeting the criteria for HCC (OPTN class 5). Not all class 5 lesions qualify for HCC MELD exception points.	Five categories range from definitely benign (category 1) to definitely HCC (category 5).
Class 5B nodules (all three criteria must be met): • Single nodule ≥ 2 cm and ≤ 5 cm • Late arterial phase enhancement • One of the following: (1) washout on portal venous/delayed phase, (2) late capsule or pseudocapsule enhancement, or (3) growth of 50% less than 6 months apart OR • Biopsy-proven HCC	Category 5 (definitely HCC): • ≥10 mm and <20 mm: mass-like, arterial phase hyperenhancement with two major features or a definite tumor within the lumen of the vein • ≥20 mm: mass-like, arterial phase hyperenhancement with one or two additional major features or a definite tumor within the lumen of the vein
Class 5A nodules: • Single nodule ≥ 1 cm and ≤ 2 cm • Late arterial phase enhancement • Both washout during later contrast phases and peripheral rim enhancement on delayed phase OR • Biopsy-proven HCC	Major features • Portal venous phase or later phase hypoenhancement with respect to the liver OR • Increase in the diameter ≥ 10 mm within 1 year
Class 5A-g nodules:* • Single nodule ≥ 1 cm and less than 2 cm • Arterial phase enhancement • Late arterial phase enhancement • Growth in maximum diameter of 50% or more on serial MRI or CT scans obtained less than 6 months apart (this does not apply to ablated lesions) Class 5T nodules (treated): May qualify for HCC MELD exception priority if • Past locoregional treatment was for an OPTN class 5 lesion or biopsy-proven HCC. • Describes any residual lesion or perfusion defect at site of prior OPTN class 5 lesion.	

For OPTN lesions, see UNOS policy 3.6.4.4[10]; for LI-RADS, the full diagnostic criteria are available from the American College of Radiology.[6]
*May meet the diagnostic criteria for HCC but does not meet the Milan criteria for MELD exception points.

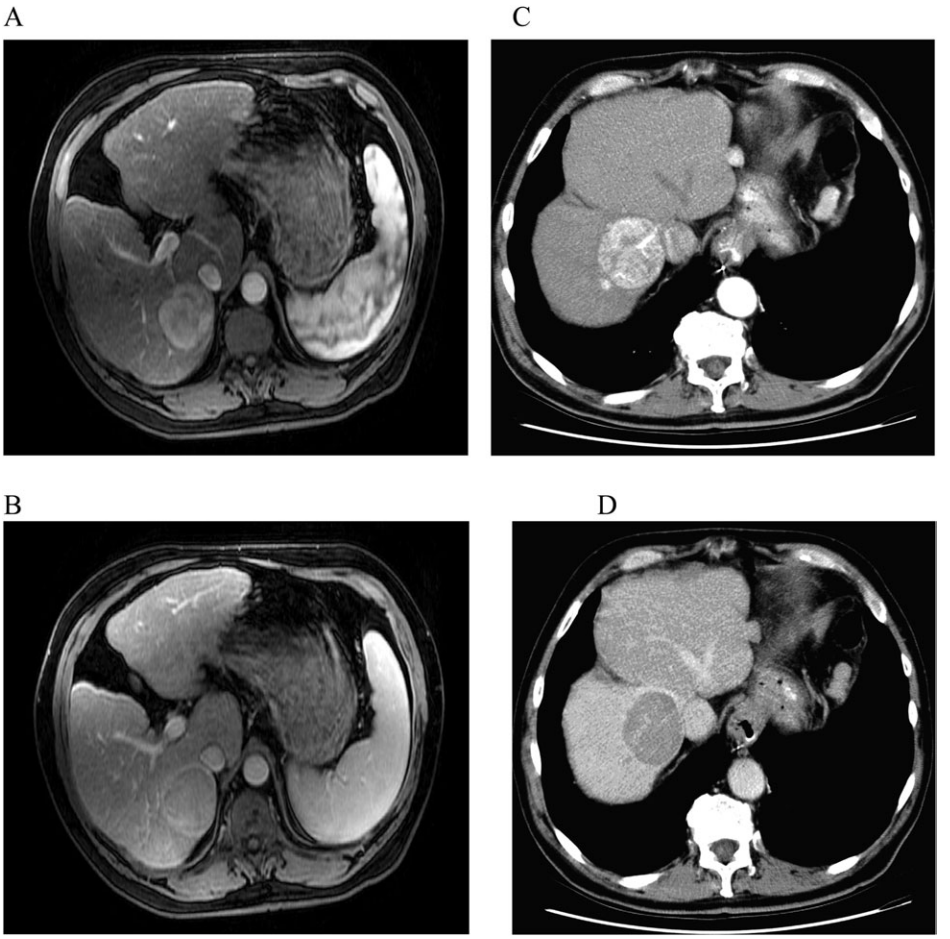

FIGURE 1. MRI scans for a liver showing (A) arterial enhancement and (B) portal venous washout and CT scans for a liver showing (C) arterial enhancement and (D) portal venous washout.

TABLE 3: Advantages and Disadvantages of CT and MRI for Diagnosing HCC

CT	MRI
Advantages	Advantages
• Faster single breath-hold total liver imaging (average < 10 seconds)	• More specific imaging characteristics for dysplastic nodules versus HCC versus regenerative nodules
• Less dependent on patient cooperation	• Hepatocyte-specific agents available
• Less complex	
• Cost	
Disadvantages	Disadvantages
• Radiation exposure	• Requires better patient cooperation for single breath-hold liver imaging (average = 15-20 seconds)
• Risk of contrast nephropathy	• Longer overall examination time (30-45 minutes)
	• Artifact caused by ascites
	• Small risk of nephrogenic systemic fibrosis in patients with renal insufficiency
	• May be contraindicated in patients with certain metal implants, claustrophobia, or pacemakers

does not meet the imaging criteria for HCC, the application of these diagnostic imaging criteria should be considered in the context of the patient's clinical circumstances.

Which Is the Better Imaging Study for HCC: MRI or CT?

The decision to proceed with CT or MRI after a liver nodule is found on ultrasound is currently predicated on center preference. Each imaging modality has its advantages and disadvantages (Table 3). There are limited data comparing CT and MRI with histology as the gold standard. An ongoing multicenter study sponsored by the American College of Radiology Imaging Network (ACRIN) and subsequently funded by the National Cancer Institute as the ACRIN 6690 liver imaging trial (NCT01082224), which is currently under way at 26 US transplant centers, should help to answer this question. In this multicenter trial, patients who are listed with HCC MELD exception points undergo both abdominal CT

and MRI until liver transplantation occurs. After transplantation, the pathologist compares the explanted liver to the CT and MRI findings. This study should help to determine whether there is a preferred imaging modality for diagnosing HCC in cirrhotic livers.

In conclusion, liver nodules that meet specific imaging characteristics for HCC do not need to be biopsied. Because the new imaging criteria are more specific than the previous criteria used to qualify patients for MELD HCC exception points, the biopsying of liver nodules, at least in liver transplant candidates, may occur more frequently. The ongoing multicenter ACRIN trial will determine whether there is a preferred cross-sectional imaging modality for diagnosing and staging HCC in cirrhotic livers. ■

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References

1. American Cancer Society. Cancer facts & figures 2011. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029771.pdf. Accessed October 2012.
2. Serag HL. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142:164–173.
3. Bruix J,Sherman M; for American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020–1022.
4. Rimola J,Forner A,Reig M,Vilana R,de Lope CR,Ayuso C, et al. Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. Hepatology 2009; 50:791–798.
5. Pomfret EA,Washburn K,Nalesnik MA,David D,Wald C,Russo M, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma. Liver Transpl 2010; 16:262–278.
6. American College of Radiology. Liver imaging reporting and data system. http://www.acr.org/Quality-Safety/Resources/LIRADS. Accessed October 2012.
7. Organ Procurement and Transplantation Network. Data. http://optn.transplant.hrsa.gov/latestData/rptData.asp. Accessed October 2012.
8. Freeman RB,Mithoefer A,Ruthazer R,Nguyen K,Schore A,Harper A, et al. Optimizing staging for hepatocellular carcinoma before liver transplantation: a retrospective analysis of the UNOS/OPTN database. Liver Transpl 2006; 12: 1504–1511.
9. Forner A,Vilana R,Ayuso C,Bianchi L,Sole M Ayuso JR, et al. Diagnosis of hepatic nodules 20mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008; 47:97–104.
10. Organ Procurement and Transplantation Network. Policy 3.6. Organ distribution: allocation of livers. http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp. Accessed October 2012.
11. Lee JM,Trevisani F,Vilgrain V,Wald C. Imaging diagnosis and staging of hepatocellular carcinoma. Liver Transpl 2011; 17(suppl 2):S34–S43.